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Lead Exposure and Human Health: Recent Data on an Ancient Problem

by Herbert L. Needleman, M.D.

Lead's toxic properties, known since Biblical times, still take a heavy toll on human health. And new data show that children are at much greater risk than had been suspected.

Relatively recent studies of both humans and experimental animals indicate that lead toxicity, or plumbism, occurs at lower doses than previously believed. As a result, more stringent controls on lead have been applied in three major areas: the workplace, the atmosphere, and the household. This removal of lead from the environment incurs the costs of applying controls, which are relatively easy to measure, and produces benefits, which are more difficult to quantify. As a result, the question of health effects at low dose has become the focus of intense controversy in recent years. The manner in which the problem of environmental lead is handled will undoubtedly serve as an important paradigm for regulating other chemical or physical agents that are at once useful and dangerous.

The Morbidity of Lead Poisoning

The symptoms of mild lead poisoning are often vague and nonspecific: headache, malaise, abdominal pain, irritability, and pallor may be the only features that are observed, and they are easily overlooked, especially in children. With increasing dosage, the brain swells and often hemorrhages, a condition known as lead encephalopathy, producing gait disturbances, stupor, coma, and convulsions. Often children with complaints stemming from the milder symptoms of plumbism are not taken to a doctor and of those who are, many are misdiagnosed. Indeed, even hospitals in areas where lead poisoning is endemic may rarely report cases because physicians are not alert to the possibility of the disease.

Many separate organ systems are affected by lead. Examples of such effects include: increased myocardial irritability, kidney dysfunction, liver dysfunction, decreased peripheral nerve conduction, and drop in the production rate of immune proteins. As is the case with many toxicants, a developing organism's brain is more vulnerable than that of an adult. Indeed, the immature brain is also vulnerable to many other stresses, including nutritional deprivation and radiation.

The damaging role of lead has been demonstrated in numerous laboratory studies:

☐ Dr. David Brown of the University of Maryland showed that rodents given lead during their first 11 days of life became poor learners, while those given the same dose from 11 to 21 days were not measurably affected. Only at *four times* the smaller dose was behavioral deficit observed in the older subjects. This different sensitivity may be due to differences with maturity in permeability of the blood brain barrier, a physiological mechanism that regulates the concentration of many compounds in the brain.

☐ Dr. Damon Averill of the Children's Medical Center and I showed that rats given doses of lead insufficient to produce anatomical changes under the light microscope have fewer and less mature synapses.

☐ Dr. R. J. Bull and his colleagues at the U.S. Environmental Protection Agency laboratory in Cincinnati demonstrated delayed brain development (late appearance of brain cytochromes), respiratory pigments in blood, and delayed synaptic development in rats prenatally exposed to lead.

History of the Problem

Lead has been mined, smelted, and compounded with benefit and hazard since antiquity. Knowledge of its toxic properties is ancient — but has been frequently ignored throughout history.

Egyptian documents written before the Hebrew Exodus show that lead was used in cosmetics, the casting of human and animal figurines, dishware, and fishing net weights. The Old Testament contains instructions for separating lead from silver ore. In the second century B.C., Nicander, a Greek poet and physician, clearly described the symptoms of lead colic. Dioscorides, in the first century A.D., wrote that ingesting lead "... causes oppression of the stomach, belly, and intestines with intense gripping pain. ... It suppresses the urine, while the body swells and acquires a leaden hue." Pliny wrote of the hazards of breathing lead fumes: "While it is being melted, the breathing passages should be protected

Poverty leads to lead exposure and developmental deficits, confounding the study of lead's effects on brain function.

Investigators must separate the effects of lead exposure from those of poverty.

... otherwise the noxious and deadly vapors of the lead furnace are inhaled." However, Pliny also advised that wine be kept in leaden vessels to avoid the toxic and bitter taste of copper. This use of lead and its widespread employment in plumbing (the Latin root of the word "plumber" is *plumbum*: "lead") have been suggested as contributing to the lower birth rate and increased prevalence of mental disturbance in the Roman ruling class, and hence to the decline of Rome (*see "Lead Poisoning: Is History Repeating Itself?" June July 1979, p. 77*).

Sir George Baker drew the attention of eighteenth-century Europe to lead's dangers when he traced the cause of the Devonshire colic epidemic to cider produced in lead vats. Baker, a resident of Devonshire, was initially reviled by local industrialists, the medical profession, and the clergy, but later was knighted and became a royal physician.

At about the same time, the Massachusetts Bay Colony was engaged in the profitable commerce of distilling rum and shipping it to North Carolina for consumption. When North Carolinian drinkers developed "the dry gripes," diagnosed as lead colic caused by rum stored in lead containers, the Massachusetts authorities responded by passing in 1723 one of the earliest public health measures in America: a state ordinance entitled "An Act for Preventing Abuses in Distilling of Rum and Other Strong Liquors with Leaden Heads or Pipes." This action was taken more to protect the Massachusetts rum industry than the North Carolinian consumers. The act prohibited the use of lead worms or still-heads and called for licensed factory inspectors. It also set penalties for violators as high as 100 pounds, which were to be divided equally among the poor of the town and the individual who informed on a violating distiller.

Benjamin Franklin left Boston for Philadelphia the year this act was promulgated, and 65 years later in a letter to Benjamin Vaughn, wrote "... I remember ... a general discourse in Boston when I was a boy of a complaint from North Carolina against New England rum, that it poisoned their people giving them the dry bellyache, with loss of the use of their limbs." Later in this letter Franklin commented on the association of colic with the drying of lead printer's type in fire and other lead-associated activities, such as painting.

Probably the first observation that children suffer from lead poisoning was made in 1891 by J.L. Gibson, an Australian ophthalmologist. He established lead as the cause of ocular palsies and neuritis in a number of children. A.J. Turner, a colleague, noted that many of these children became ill after changing residence, but he was unable to specify the source and characterized the lead poisoning as a "toxicity of habitation." Gibson determined in 1904 that many of his patients were nail-biters or thumb-suckers, and suggested the origin of the lead to be the paint in the children's homes. While all children tend to mouth foreign substances, it was recognized that some persist in the habit and can take in huge doses of lead in this fashion. At this time childhood lead poisoning was considered primarily a disease of urban children with paint as its major, if not only, source.

But this conclusion ignored other important observations. At the turn of the century, British factory inspectors reported startlingly high levels of barrenness, stillbirths, and first-year infant death among women exposed to lead through the manufacture of pottery.

It was not yet known that lead in pregnant mothers could affect the development of their infants' brains, but data pointing in this direction did exist. In Glasgow, where the water is soft and often stored in lead-lined tanks, Professor Abraham Goldberg of the University of Glasgow showed an increased incidence of mental retardation in children born in homes where the water supply contained excessive lead. Some blood samples from retarded children drawn at one week of life had significantly higher lead levels than did the blood of control subjects.

Modern Sources of Environmental Lead

A considerable portion of dietary lead originates in pesticide sprays, cooking utensils, and solder in cans. Lead in water may be a source for individual households if the water is soft (of low mineral content) and acidic, and the pipes are made of lead (conditions found in some homes in older Eastern cities such as Cambridge and Boston).

Lead put into the air by obvious stationary sources such as smelters is a major problem for nearby communities, but automobile emissions are a much greater contributor. In 1975, based on the use of lead-based gasoline additives, approximately 150,000 metric tons of lead were emitted into the atmosphere over the continental U.S. After combustion, most of the lead leaves the tailpipe as lead bromide. Larger particles fall out rather promptly into the dirt and soil by the roadside. Smaller particles tend to stay airborne and travel farther.

Lead exposure has long been recognized as a threat to smelter workers, battery plant operators, painters, and ship breakers. In such workplaces lead dust permeates the air and blankets the ground. A substantial part of that lead is inspired and absorbed.

Pathways into the Body

Lead enters the human body through two major routes: the gastrointestinal (GI) tract and the lungs. The contribution of each source to a person's lead burden and physiological impact varies especially with age and environment. Obviously, a toll collector at the Lincoln Tunnel will have a different partition of sources than either a battery worker or an inner-city child. Of the portion of lead introduced into the GI tract of an adult, about 10 per cent is absorbed; however, a child's gut is much more permeable and may absorb as much as 50 per cent. About 40 per cent of small particles of inspired lead (less than 1 micrometer in diameter) is retained and absorbed in the lungs. Some evidence exists that suggests a higher proportion of inspired lead is absorbed into children's lungs.

Lead paint poisoning continues to be a serious problem for children, despite the fact that lead was phased out in pigment in the 1940s and then banned as a drying agent in the 1970s. Many houses have paint over 40 years old, much of which is flaking and peeling. Some children, for not well understood reasons, persist in the habit of eating foreign substances, and some develop a specific taste for lead. Enormous quantities can be ingested in this manner. Even if the paint does not peel, it slowly weathers and chalks, and thus contributes to lead in dust. Ordinary urban dust contains surprisingly high amounts of lead (up to 1 per cent), and the typical hand-to-mouth behavior of children can result in significant absorption.

It was once assumed that when a child recovered from lead poisoning and the symptoms subsided, brain function returned to normal. But this belief was refuted in 1943 by Drs. Randolph Byers and Elizabeth Lord at the Boston Children's Hospital. They studied 20 children thought to have recovered from acute lead intoxication and found that 19 were behavior-disordered or failing in school and that most had sensory-motor defects. They raised, perhaps for the first time, the troubling question of whether undiagnosed lead poisoning was a source of some school and behavior problems.

In Pursuit of Epidemiologic Data

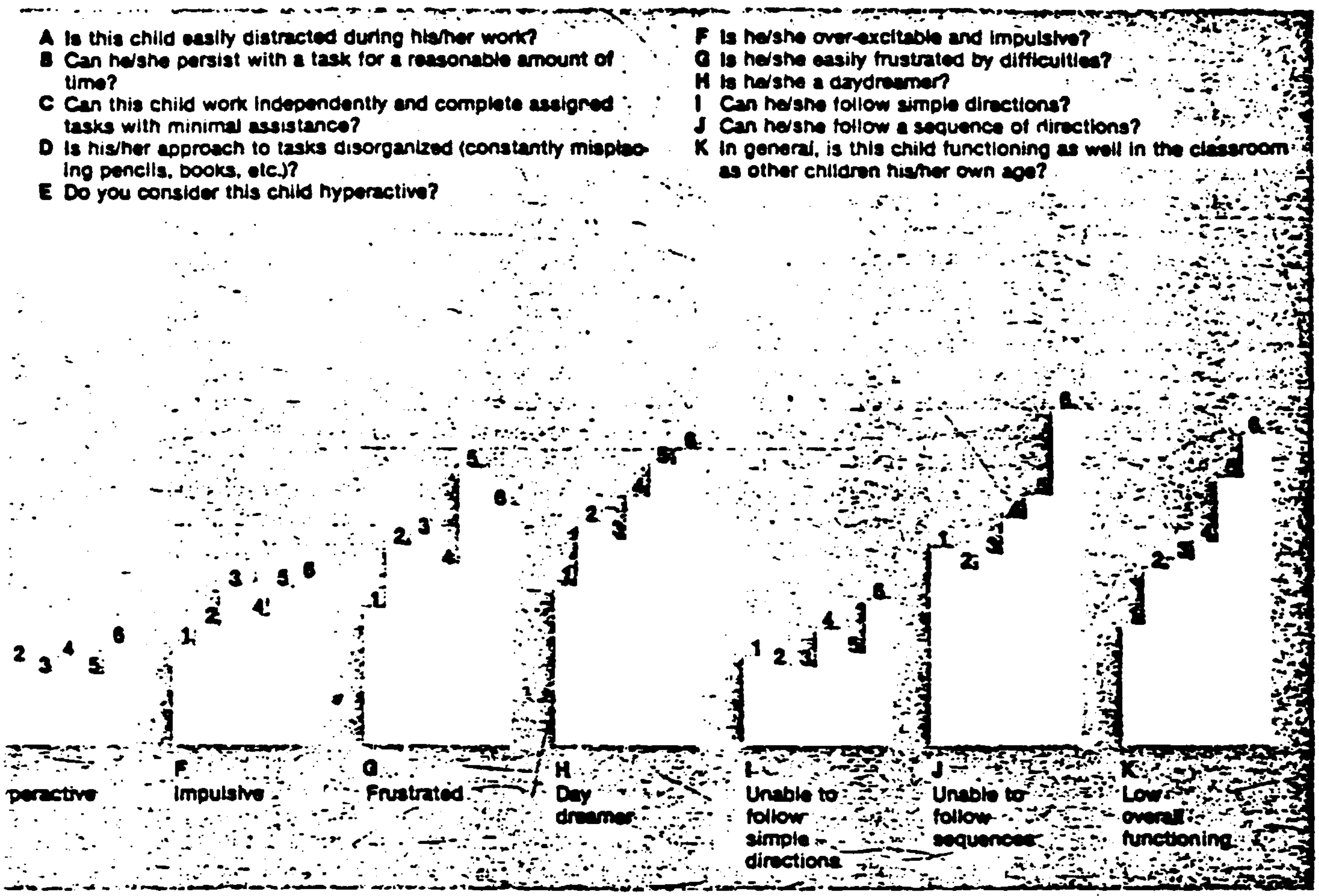
The growing realization over the past ten years that many thousands of children have elevated blood lead levels has directed considerable attention to two questions:

☐ Does lead, at doses below those that produce symptoms dramatic enough to put children in the hospital, cause impairment in neuropsychologic function?

☐ Can low levels of lead in the body cause slight impairment of brain function that could be manifested as learning disabilities, detectable brain disorders, or school failure?

Since 1972 physicians have conducted a large number of epidemiologic studies of lead-exposed children. The authors of most studies classify children into "exposed" or "nonexposed" groups by measuring the amount of lead in their bloodstream. The children are then evaluated on a number of psy-

The distribution of eleven measures of negative behavior, as rated by teachers for 2,146 first- and second-grade children in Chelsea and Somerville, Mass., in relation to the concentration of lead in the students' deciduous ("baby") teeth. Note the striking positive correlation between increasing amounts of dentine lead and the prevalence of negative behavior. (*Data: H. L. Needleman et al. in the* New England Journal of Medicine)



chological performance or competence tasks, and "high-lead" and "low-lead" subjects are then compared. Dr. Bridgette de la Burde and M. S. Choate in Virginia, Dr. Philip Landrigan and coworkers at the Center for Disease Control, and Joseph Perino and Claire Ernhart at Hofstra University found that children with increased lead exposure clearly performed less ably than nonexposed children. But others — including Richard Lansown and coworkers at the Great Ormond Street Hospital (formally the Hospital for Sick Children) in London, Dr. David Kotok and coworkers at Yale-New Haven Hospital, and Dr. Robert W. Baloh and coworkers at UCLA — were unable to detect a difference.

Among the reasons for discrepancies in the conclusions of these studies are certain methodological flaws that are common to many epidemiologic investigations. The four most common are these:

☐ *Inadequate classification*. The presence of lead in the blood is only a short-term measure of exposure. Lead in the blood of a child may drop to normal levels after the child suffers a severe dose.

☐ *Selection bias*. In a free society, parents and children may decline to participate in an epidemiologic study. Their choice may be related to the outcome of interest. For example, the parents of children suspected of being handicapped might not wish to have the children examined. Such a survey would then miss the children with the greatest deficit.

☐ *Insensitive measures of outcome*. The detection of subtle impairment requires sensitive tools. Some studies that employed rather coarse screening measures have not discovered differences.

☐ *Lack of attention to other variables that affect outcome*. Many other factors can influence the development of children, and some of these can segregate with lead. While lead is not exclusively a problem for children of poor families, it is true that such children generally experience more lead exposure. Factors other than lead poisoning assault the de-

The time in milliseconds needed for 140 first- and second-grade children to react to a command stimulus (a buzzer), with varying delays between a warning signal (the word "ready") and the stimulus. Each child had six trials in each block of testing. Note that the 53 high-lead children were consistently slower to react than were the 87 low-lead children. (*Data: H.L. Needleman et al. in the New England Journal of Medicine*)

velopment of the poor: inferior nutrition, increased infections, and less-than-adequate schools.

My group at the Children's Hospital Medical Center in Boston set out specifically to address these four methodological issues in a large study of children considered asymptomatic for lead. To avoid the shortcoming of using blood lead levels as an indicator of plumbism, I needed a tissue that accurately traced the past history of exposure to lead in older children. Lead is deposited in bone, but bone biopsies involve risk and discomfort. It occurred to me, as it had to others, that deciduous teeth would provide a universal, spontaneous, and painless bone biopsy of children at the particular age of interest.

I then collected deciduous teeth and measured their lead levels. Results left no doubt that dental lead was elevated in lead-poisoned children — and in children who lived in "the lead belt," the zone of the city where lead poisoning is endemic.

In our study, my colleagues and I collected teeth from 70 per cent of children attending ordinary — nonremedial — first grade and second-grade classes in Chelsea and Somerville, Massachusetts. Each child was rated by the teacher (who of course did not know the child's lead level) on 11 measures of classroom behavior (*see graph on p. 43*). Children with the highest and lowest dentine lead levels then were invited to participate in our intensive neurobehavioral study. If they came from English-speaking households, were full-term babies, had experienced no serious head injuries, and were never previously diagnosed as having excessive lead exposure, they were admitted, with parental approval, to the study. (We later compared dentine lead and the 11 measures of classroom behavior of children included and excluded from the neuropsychologic study. We found the children included in the study did not differ in these respects from those who did not participate.)

Each child was individually tested by examiners who were unaware of the child's lead status. Part of the three-hour neuropsychologic examination included having mothers complete a comprehensive questionnaire and take an IQ test. We then compared "high-lead" and "low-lead" children on a large number of variables. We identified numerous nonlead variables that did not correlate with dentine lead level, such as height, weight, head circumference, gender, and race. Other nonlead variables such as size of family, age, education, and IQ of mothers and socioeconomic status of fathers that did correlate with dentine lead levels were controlled in the final biostatistical evaluation by a procedure known as the analysis of covariance.

Our overall findings clearly linked lead and behavioral problems. High-lead children were found to perform significantly less well on the Wechsler Intelligence Scale (especially on the verbal tests), on a number of tests of auditory and language skills, on the ability to maintain attention, and on classroom behavior as previously measured by teachers' ratings. Indeed, when the entire sample of 2,146 students (92 per cent of the 2,335 children who submitted teeth) were classified according to dental lead and the teachers' reports of each negative behavior, the increase in these behaviors appeared to be clearly related to the dose of lead — *and there appeared to be no "threshold" for this effect.*

Following our study, Drs. Hrdina and Winnecke of Dusseldorf found substantially the same relationship between dentine lead and behavior in a smaller sample of German school-age children.

Some critics have asked whether variables such as parental IQ and education may not have been the major determinants in the outcome of our study, and whether those children who were prone to put things in their mouths — behavior called "mouthing" — which led them to have higher lead levels were not a priori impaired. But in our study, we measured and allowed for the contribution of nonlead variables such as parental IQ and quality of education. And the effect of lead on neurobehavioral function clearly persisted after controlling for those nonlead variables. We compared the intelligence and language performance of children with reported excessive mouthing behavior and found no significant differences from nonmouthing children who had similar levels of lead in their teeth.

Other compelling responses to the critics come from laboratory studies conducted with animals, where such rearing variables as maternal IQ and mouthing behavior can be completely and systematically controlled:

☐ Philip Bushnell and Robert Bowman at the Wisconsin Primate Laboratory recently demonstrated slowed visual learning in young rhesus monkeys whose blood levels did not exceed 40 to 60 micrograms of lead per deciliter of blood.

☐ Ellen Silbergeld and coworkers at the National Institutes of Health have shown that lead interferes with neurochemical function at the subcellular level by altering the concentration and flow of sodium and calcium ions. These changes may then affect the activity of cholinergic and dopaminergic neurons,

Souvenir of the epidemiological study in which lead levels in deciduous teeth were found to correlate positively with negative behavior in the classroom. A button was given to each of the participating first-and second-graders. *(Photo: Leonard A. Phillips)*

which can retard brain function.

☐ David Taylor and coworkers at the University of Colorado Medical Center in Denver have shown that lead micropipetted in minute quantities into rat brains decreases norepinephrine-mediated inhibition, and thus affects central neurotransmission.

☐ A number of other workers have demonstrated teratogenic properties (factors that produce birth defects) of lead given during pregnancy to experimental animals.

Recent Attempts at Controls

One of the stagnating — if not paralyzing — activities of regulatory agencies and some industries has been repeated attempts to shift the blame for environmental lead to a source outside their individual responsibility. Such actions have led to an interesting phenomenon in which the lead industry indicts paint and paint eating as the major source of serious lead exposure in the U.S., while the Department of Housing and Urban Development and real estate interests go to considerable lengths to downplay the role of lead-based paint as a threat to children. Paint manufacturers agree that paint could be hazardous, but extend their immediate concern only to paint already applied and not to unsold paint in cans on store shelves.

In the 1960s, U.S. cities and poor people reentered the zeitgeist. Epidemiologic data collected during that period indicated that as many as 10 per cent of our children had blood lead levels close to the range defined as toxic (above 60 micrograms of lead per deciliter of blood). A coalition of inner-city mothers (some of whose children had been lead-poisoned), public interest lawyers, and a few physicians brought these data into public scrutiny, and two major legislative thrusts resulted:

☐ In 1971 Congress passed the Lead Paint Poisoning Prevention Act, which established early detection as a strategy, provided for limited environmental control, called for further research, and defined the toxic level of lead in paint to be 0.5 per cent by weight. In 1973 the act was amended, lowering the permissible level in paint to 0.06 per cent. In 1975 the Consumer Product Safety Commission ruled that any paint with lead concentrations greater than 0.06 per cent by weight was unsuitable for household use.

☐ In 1970 the Environmental Protection Agency was mandated by Congress under the Clean Air Act to prepare air standards on certain hazardous substances, including lead. But by 1975 the EPA had not acted. A suit brought by the Natural Resources Defense Council against the EPA was upheld by the courts, which ordered the EPA to prepare the standards. The first draft of the scientific document issued by the EPA asserted that a national airborne lead standard of 5 micrograms of lead per cubic meter of air was adequate to protect public health. But this concentration was two and a half times greater than previous EPA estimates and was at considerable variance with the opinion of many non-EPA scientists. After a stormy series of public hearings, the EPA staff was advised by its scientific advisory board not to revise the draft, but to destroy it and begin anew. After two more drafts, the EPA recommended a level of 1.5 micrograms per cubic meter, which was the standard later promulgated by EPA administrator Douglas Costle — and which is currently the issue upon which EPA is being sued by the Lead Industries Association.

The Lead Outlook

Many new data have been accumulated in the past decade regarding the dangers of lead to humans and especially to children. Analysis of these data indicate that the effects of lead are found at lower levels of exposure than were previously recognized, and that any apparent threshold of adverse biologic effects varies with the sensitivity and rigor of the investigative method. It seems likely that the standard for acceptable exposure to lead, given the history of scientific progress, will require further downward revision as new information is gathered and evaluated.

Further Reading

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